Q11 Development and Manufacture of Drug Substances

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ICH DRAFT:

Topic Reference: Q11

Subject: Development and Manufacture of Drug Substances (chemical entities and biotechnological/biological entities)

Draft No. Step 2 Document Dated: 28 April 2011

Table of Contents

1 Introduction

This guideline describes approaches to developing process and drug substance understanding and also provides guidance on what information should be provided in CTD sections 3.2.S.2.2 – 3.2.S.2.6. It provides further clarification on the principles and concepts described in ICH guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality Systems (Q10) as they pertain to the development and manufacture of drug substance.

A company can choose to follow different approaches in developing a drug substance. For the purpose of this guideline, the terms "traditional" and "enhanced" are used to differentiate two possible approaches. In a traditional approach, set points and operating ranges for process parameters are defined and the drug substance control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria. In an enhanced approach, risk management and more extensive scientific knowledge are used to select process parameters and unit operations that impact critical quality attributes (CQAs) for evaluation in further studies to establish any design space(s) and control strategies applicable over the lifecycle of the drug substance. As discussed in ICH Q8 for drug product, a greater understanding of the drug substance and its manufacturing process can create the basis for more flexible regulatory approaches. The degree of regulatory flexibility is generally predicated on the level of relevant scientific knowledge provided in the application for marketing authorisation.

Traditional and enhanced approaches are not mutually exclusive. A company can use either a traditional approach or an enhanced approach to drug substance development, or a combination of both.

2 Scope

This guideline is applicable to drug substances as defined in the Scope sections of ICH Guidelines Q6A and Q6B, but might also be appropriate for other types of products following consultation with the appropriate regulatory authorities. It is particularly relevant to the preparation and organisation of the contents of sections 3.2.S.2.2 – 3.2.S.2.6 of Module 3 of the Common Technical Document (ICH M4Q). The guideline does not apply to contents of submissions during the clinical research stages of drug development. Nevertheless, the development principles presented in this guideline are important to consider during the investigational stages.

Regional requirements for post-approval changes are not covered by this guideline.

3 Manufacturing Process Development

3.1 General Principles

The goal of manufacturing process development for the drug substance is to establish a commercial manufacturing process capable of consistently producing drug substance of the intended quality.

3.1.1 Drug Substance Quality Link to Drug Product

The intended quality of the drug substance should be determined through consideration of its use in the drug product as well as from knowledge and understanding of its physical, chemical, biological, and microbiological properties or characteristics, which can influence the development of the drug product (e.g., the solubility of the drug substance can affect the choice of dosage form). The Quality Target Product Profile (QTPP) and potential CQAs of the drug product (as defined in ICH Q8) can help identify potential CQAs of the drug substance. Knowledge and understanding of the CQAs can evolve during the course of development.

3.1.2 Process Development Tools

Quality Risk Management (QRM, as described in ICH Q9) can be used in a variety of activities including assessing options for the design of the manufacturing process, assessing quality attributes and manufacturing process parameters, and increasing the assurance of routinely achieving acceptable quality results. Risk assessments can be carried out early in the development process and repeated as greater knowledge and understanding become available. It is neither always appropriate nor always necessary to use a formal risk management process (using recognised tools and/or internal procedures, e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable.

Knowledge management (as described in ICH Q10) can also facilitate manufacturing process development. In this context, potential sources of information can include prior knowledge and development studies. Prior knowledge can include established biological, chemical and engineering principles and applied manufacturing experience. Data derived from relevant prior knowledge, including platform manufacturing (see glossary) can be leveraged to support development of the commercial process and expedite scientific understanding.

3.1.3 Approaches to Development

ICH Q8 recognises that “Strategies for product development vary from company to company and from product to product. The approach to, and extent of, development can also vary and should be outlined in the submission.” These concepts apply equally to the development of the drug substance manufacturing process. An applicant can choose either a traditional approach or an enhanced approach to drug substance development, or a combination of both.

Manufacturing process development should include, at a minimum, the following elements:

- Identifying potential CQAs associated with the drug substance so that those characteristics having an impact on product quality can be studied and controlled;
- Defining an appropriate manufacturing process;
- Defining a control strategy to ensure process performance and drug substance quality (see Section 6 on Control Strategy).

An enhanced approach to manufacturing process development would additionally include the following elements:

- A systematic evaluation, understanding and refining of the manufacturing process, including;
    - Identifying, through e.g. prior knowledge, experimentation and risk assessment, the material attributes and process parameters that can have an effect on drug substance CQAs;
    - Determining the functional relationships that link material attributes and process parameters to drug substance CQAs;
- Using the enhanced approach in combination with QRM to establish an appropriate control strategy which can, for example, include a proposal for a design space(s) and/or real-time release testing (RTRT).

The increased knowledge and understanding obtained from taking an enhanced approach could facilitate continual improvement and innovation throughout the product lifecycle (see ICH Q10).

3.1.4 Drug Substance Critical Quality Attributes

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. Potential drug substance CQAs are used to guide process development. The list of potential CQAs can be modified as drug substance knowledge and process understanding increase.

Drug substance CQAs typically include those properties or characteristics that affect identity, purity, biological activity and stability. When physical properties are important with respect to *in vivo* performance or drug product manufacture, these can be designated as CQAs. In the case of biotechnological/biological products, most of the CQAs of the drug product are associated with the drug substance and thus are a direct result of the design of the drug substance or its manufacturing process.

Impurities are an important class of potential drug substance CQAs because of their potential impact on drug product safety. For chemical entities, impurities can include organic impurities (including potential genotoxic impurities), inorganic impurities, for example metal residues, and residual solvents (see ICH Q6A, Q3A, and Q3C). For biotechnological/biological products, impurities may be process-related or product-related (see ICH Q6B). Process-related impurities include: cell substrate-derived impurities (e.g., Host Cell Proteins and DNA); cell culture-derived impurities (e.g., media components); and downstream-derived impurities (e.g., column leachables). CQAs for biotechnology/biological products should also include consideration of contaminants, as defined in Q6B, including all adventitiously introduced materials not intended to be part of the manufacturing process (e.g., adventitious viral, bacterial, or mycoplasma contamination).

The identification of CQAs for complex products can be challenging. Biotechnological/biological products, for example, typically possess such a large number of quality attributes that it might not be possible to fully evaluate the impact on safety and efficacy of each one. Risk assessments can be performed to rank or prioritise quality attributes. Prior knowledge can be used at the beginning of development and assessments can be iteratively updated with development data (including data from non-clinical and clinical studies) during the lifecycle. Knowledge regarding mechanism of action and biological characterisation, such as studies evaluating structure-function relationships, can contribute to the assessment of risk for some product attributes.

3.1.5 Linking Material Attributes and Process Parameters to Drug Substance CQAs

The manufacturing process development program should identify which material attributes (e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters should be controlled. Risk assessment can help identify the material attributes and process parameters with the potential for having an effect on drug substance CQAs. Those material attributes and process parameters that are found to be important to drug substance quality should be addressed by the control strategy.

The risk assessment to define the control strategy of materials upstream from the drug substance can include an assessment of manufacturing process capability, attribute detectability, and severity of impact as they relate to drug substance quality. For example, when assessing the link between an impurity in a raw material or intermediate and drug substance CQAs, the ability of the drug substance manufacturing process to remove that impurity should be considered in the assessment. The risk related to impurities can usually be controlled by specifications for raw material/intermediates and/or robust purification capability in downstream steps. The risk assessment can also identify material attributes for which there are inherent limitations in detectability (e.g., viral safety) or inadequate purification capability. In these cases, such upstream material attributes should be considered drug substance CQAs.

Using a traditional approach, material specifications and process parameter ranges can be based primarily on batch process history and univariate experiments. An enhanced approach can lead to a more thorough understanding of the relationship of material attributes and process parameters to CQAs and the effect of interactions. Example 1 illustrates the development of process parameters using prior knowledge and chemistry first principles.

Risk assessment can be used during development to identify those parts of the process likely to impact potential CQAs. Further risk assessments can be used to focus development work in areas where better understanding of the link between process and quality is needed. Using an enhanced approach, the determination of appropriate material specifications and process parameter ranges could follow a sequence such as the one shown below:

- Identify potential sources of process variability;

- Identify the material attributes and process parameters likely to have the greatest impact on drug substance quality. This can be based on prior knowledge and risk assessment tools;
- Design and conduct experiments and/or mechanistic studies (e.g., multivariate design of experiments, simulations, modelling) to identify and confirm the links and relationships of material attributes and process parameters to drug substance CQAs;
- Analysis and assessment of the data to establish appropriate ranges, including establishment of a design space if desired.

Small-scale models can be developed and used to support process development studies. The development of a model should account for scale effects and be representative of the proposed commercial process. A scientifically justified model can enable a prediction of product quality, and can be used to support the extrapolation of operating conditions across multiple scales and equipment.

3.1.6 Design Space

The considerations for design space addressed in ICH Q8 for an enhanced approach to the development of the drug product are equally applicable to drug substance. The ability to accurately assess the significance and effect of the variability of material attributes and process parameters on drug substance CQAs, and hence the limits of a design space, depends on the extent of process and product understanding. In some cases, prior knowledge can be used to support development of a design space. Irrespective of whether the manufacturing process of a product has been developed using prior knowledge the manufacturing process should be appropriately validated (see Process Validation/Evaluation Section 7).

For chemical entity design space development, a major focus is knowledge of formation, fate, and purge of impurities through every step of a manufacturing process. It is important to understand the formation, fate (whether the impurity reacts and changes its chemical structure), and purge (whether the impurity is removed via crystallisation, extraction, etc.) as well as their relationship to the resulting impurities that end up in the drug substance as CQAs. All steps (or unit operations) should be evaluated to establish appropriate acceptance criteria for impurities as they progress through multiple process operations.

3.2 Submission of Manufacturing Process Development Information

The information provided on the development of the drug substance manufacturing process (primarily in section 3.2.S.2.6 of the application) should identify significant changes during process development, link relevant drug substance batches with the developmental stage of the manufacturing process used to prepare them, and explain how prior knowledge, risk assessments, and experimental studies (e.g., modelling, simulations, engineering and scientific principles) were used to establish important aspects of the manufacturing process and control strategy. The significance of a drug substance manufacturing change during development should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). Process development information should be logically organised and easy to understand. Manufacturers can present process development information in a number of different ways, but some specific recommendations are provided below for consideration.

3.2.1 Overall Process Development Summary

It is recommended that the manufacturing process development section begin with a narrative summary that describes important milestones in the development of the process and explains how they are linked to assuring that the intended quality of the drug substance is achieved. The following should be included in the summary:

- List of drug substance CQAs;
- Brief description of the stages in the evolution of the manufacturing process and control strategy;
- Brief description of the material attributes and process parameters that impact drug substance CQAs;
- Brief description of the development of any design spaces.

Following the Overall Process Development Summary, the manufacturing process development section should include more comprehensive information, as recommended below.

3.2.2 Drug Substance CQAs

The CQAs of the drug substance should be listed, and the rationale for designating these properties or characteristics as CQAs should be provided. In some cases, it might be appropriate to explain why other properties or characteristics that might be considered potential CQAs are not included in the list of CQAs. Links or references should be provided to information submitted elsewhere in the submission (e.g., 3.2.S.3.1, Elucidation of Structure and other Characteristics) that supports the designation of these properties or characteristics as CQAs. Some discussion of drug substance CQAs as they relate to drug product CQAs can be appropriate in the pharmaceutical development section of the application (e.g., 3.2.P.2.1, Components of the Drug Product).

3.2.3 Manufacturing Process History

A description and discussion should be provided of significant changes made to the manufacturing process or site of manufacture of drug substance batches used in support of the marketing application (e.g., those used in nonclinical or clinical studies or stability studies in support of a marketing authorisation) and, if available, production-scale batches. The description should follow a chronological sequence ending with the proposed commercial process.

The reason for each significant change should be explained, together with an assessment of its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). Batch information (batch size or scale, site and date of manufacture, route and process used, and intended purpose (e.g., in a specified toxicology or clinical study)) and supporting data from comparative analytical testing on relevant drug substance batches should be provided or referenced (e.g., batch analysis section 3.2.S.4.4).

For biotechnological/biological products, the manufacturing process history section should include a discussion of comparability during development as described in ICH Q5E. A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance and the corresponding drug product can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included.

3.2.4 Manufacturing Developmental Studies

The studies and risk assessments used to establish important aspects of the commercial manufacturing process and control strategy cited in the application should be listed (e.g., in tabular form). The purpose or end use of each cited study or risk assessment should be provided.

Each cited study or risk assessment should be summarised with a level of detail sufficient to convey an understanding of the purpose of the study, the data collected, how it was analysed, the conclusions reached, and the impact of the study on the manufacturing process or further development of the manufacturing process. The particular parameters and ranges studied should be described and discussed in relation to the proposed operating conditions for the commercial manufacturing process (as described in 3.2.S.2.2). The risk assessment tools and study results on which a design space is based should be adequately described. Example 2 shows a possible communication tool for risk ranking of parameters. Where development refers to specific prior knowledge, the relevant information and data should be provided and, where appropriate, the relevance to the particular drug substance should be justified.

Small-scale models used to support process development studies should be described.

4 Description of Manufacturing Process and Process Controls

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls (see ICH M4Q (3.2.S.2.2).

The description of the manufacturing process should be provided in the form of a flow diagram and sequential procedural narrative. The in-process controls for each step or stage of the process should be indicated in the description. Scaling factors should be included for manufacturing steps intended to span multiple operational scales when the process step is scale dependent. Any design spaces in the manufacturing process should be included as part of the manufacturing process description. Example 3 gives an example of the presentation of a design space for a biotechnological product.

To facilitate the approval of a design space for a complex product, such as a biotechnological/biological product, an applicant can choose to provide information on how movements within the design space will be managed post approval. This could help the reviewer understand how residual risk will be managed.

Many biotechnological/biological products have complex upstream processes and use splitting and pooling to create a drug substance. An explanation of how batches of drug substance are defined by the manufacturer (e.g., splitting and pooling of harvests or intermediates), should be provided. Details of batch size or scale and batch numbering should be included.

5 Selection of Starting Materials and Source Materials

5.1 General Principles

5.1.1 Selection of Starting Materials for Synthetic Drug Substances

The following general principles should be considered in determining where the drug substance manufacturing process begins (i.e., in selecting starting materials).

- In general, changes in material attributes or operating conditions that occur near the beginning of the manufacturing process have lower potential to impact the quality of the drug substance;
    - The relationship between risk and number of steps from the end of the manufacturing process is the result of two factors, one concerning the physical properties of the drug substance and the other concerning the formation, fate, and purge of impurities. The physical properties of a drug substance are determined during the final crystallisation step and subsequent operations (e.g., milling, micronising, transport), all of which occur at the end of the manufacturing process. Impurities introduced or created early in the manufacturing process typically have more opportunities to be removed in purification operations (e.g., washing, crystallisation of isolated intermediates) than impurities generated late in the manufacturing process, and are therefore less likely to be carried into the drug substance. However, in some cases (e.g., when peptides or oligonucleotides are synthesised on a solid support), there is a more limited relationship between risk and number of steps from the end of the manufacturing process;
- Regulatory authorities assess whether the controls on the drug substance and drug substance manufacturing process can be considered adequate, including whether there are appropriate controls for impurities. To conduct this assessment, enough of the drug substance manufacturing process should be described in the application for regulatory authorities to understand how impurities are formed in the process, how changes in the process could affect the formation, fate, and purge of impurities, and why the proposed control strategy is suitable for the drug substance manufacturing process. This will typically include a description of multiple chemical transformation steps;
- Manufacturing steps that impact the impurity profile of the drug substance should normally be included in the manufacturing process described in section 3.2.S.2.2 of the application;
- Each branch of a convergent drug substance manufacturing process begins with one or more starting materials. The GMP provisions described in ICH Q7 apply to each branch beginning with the first use of a starting material. Performing manufacturing steps under GMP together with an appropriate control strategy provides assurance of quality of the drug substance;

- A starting material should be a substance of defined chemical properties and structure. Non-isolated intermediates are usually not considered appropriate starting materials;

- A starting material is incorporated as a significant structural fragment into the structure of the drug substance. “Significant structural fragment” in this context is intended to distinguish starting materials from reagents, solvents, or other raw materials. Commonly available chemicals used to create salts, esters or other simple derivatives should be considered reagents.

All the general principles above should be considered in selecting Starting Material(s), rather than strictly applying each general principle in isolation (see Example 4).

5.1.2 Selection of Starting Materials for Semi-synthetic Drug Substances

For purposes of this guideline, a semi-synthetic drug substance is one in which the structural constituents have been introduced by a combination of chemical synthesis and elements of biological origin (e.g., obtained from fermentation or by extraction from botanical material). In some cases, it might be appropriate for the applicant to describe the manufacturing process starting from the source material (microorganism or botanical material). However, if it can be demonstrated that one of the isolated intermediates in the synthetic process complies with the principles outlined above for the selection of starting materials for synthetic drug substances, that isolated intermediate can be proposed as the starting material. The applicant should specifically evaluate whether it is possible to analytically characterise the proposed starting material, including its impurity profile, and whether the fermentation or botanical material and extraction process impact the impurity profile of the drug substance. Risks from microbial and other contamination should also be addressed.

5.1.3 Selection of Source Materials for Biotechnological/Biological Products

Cell banks are the starting point for manufacture of biotechnological/biologics products. Guidance appropriate for cell banks is contained in ICH Q5A, Q5B, and Q5D.

5.2 Submission of Information for Starting Material or Source Material

Applicants should identify all proposed starting materials or source materials and provide appropriate specifications. Proposed starting materials should be justified.

5.2.1 Justification of Starting Material Selection for Synthetic Drug Substances

The applicant should provide a justification for how each proposed starting material is appropriate in light of the general principles for the selection of starting materials outlined above in Section 5.1.1. This can include information on:

- The ability of analytical procedures to detect impurities in the starting material;

- The fate and purge of those impurities and their derivatives in subsequent processing steps;

- How the proposed specification for each starting material will contribute to the control strategy;

The applicant should provide, as part of the justification, a flow diagram outlining the current synthetic route(s) for the manufacture of the drug substance, with the proposed starting materials clearly indicated. Changes to the starting material specification and to the synthetic route from the starting material to final drug substance are subject to regional, post-approval change requirements. In addition, regional requirements concerning starting material suppliers may also be applicable.

An applicant generally need not justify the use of a commercially available chemical as a starting material. A commercially available chemical is usually one that is sold as a commodity in a pre-existing, non-pharmaceutical market in addition to its proposed use as starting material. Chemicals produced by custom syntheses are not considered to be commercially available. If a chemical from a custom synthesis is proposed as a starting material, it should be justified in accordance with the general principles for the selection of starting materials outlined above in Section 5.1.1.

In some instances, additional purification steps might be called for to ensure the consistent quality of a commercially available starting material. In these instances, the additional purification steps should be included as part of the description of the drug substance manufacturing process. Specifications should normally be provided for both incoming and purified starting material.

5.2.2 Justification of Starting Material Selection for Semi-Synthetic Drug Substances

If an isolated intermediate is proposed as the starting material for a semi-synthetic drug substance, the applicant should provide a justification that explains how the proposed starting material complies with the general principles for the selection of starting materials outlined above in Section 5.1.1. Otherwise, the applicant should describe the manufacturing process starting from the source material (microorganism or botanical material) and the source materials should be appropriately qualified.

5.2.3 Qualification of Source Materials for Biotechnological/Biological Products

Guidance is contained in ICH Q5A, Q5B and Q5D.

6 Control Strategy

6.1 General Principles

A control strategy is a planned set of controls, derived from current product and process understanding, that assures process performance and product quality (ICH Q10). Every drug substance manufacturing process, whether developed through a traditional or an enhanced approach (or some combination thereof), has an associated control strategy.

A control strategy can include, but is not limited to, the following:

- Controls on material attributes (including raw materials, starting materials, intermediates, reagents, primary packaging materials for the drug substance, etc.);
- Controls implicit in the design of the manufacturing process (e.g., sequence of purification steps (Biotechnological/Biological Products), or order of addition of reagents (Chemical Products));

- In-process controls (including in-process tests and process parameters);
- Controls on drug substance (e.g., release testing).

6.1.1 Approaches to Developing a Control Strategy

A control strategy can be developed through a combination of approaches, utilising the traditional approach for some CQAs, steps, or unit operations, and a more enhanced approach for others.

In a traditional approach to developing a manufacturing process and control strategy, set points and operating ranges are typically set narrowly based on the observed data to ensure consistency of manufacture. More emphasis is placed on assessment of CQAs at the stage of the drug substance (i.e., end-product testing). The traditional approach provides limited flexibility in the operating ranges to address variability (e.g., in raw materials).

An enhanced approach to manufacturing process development generates better process and product understanding than the traditional approach, so sources of variability can be identified in a more systematic way. This allows for the development of more meaningful and efficient parametric, attribute, and procedural controls. The control strategy might be developed through several iterations as the level of process understanding increases during the product lifecycle. A control strategy based on an enhanced approach can provide for flexibility in the operating ranges for process parameters to address variability (e.g., in raw materials).

6.1.2 Considerations in Developing a Control Strategy

In either the traditional or enhanced approach, the control strategy can include an in-process determination that a CQA is within an appropriate limit, range or distribution in lieu of testing the final drug substance. Any approach other than testing the final drug substance should provide at least the same level of assurance of drug substance quality. When considering such an approach, applicants should determine whether there are any downstream factors that might impact the quality of the drug substance, such as temperature changes, oxidative conditions, light, ionic content, and shear.

When developing a control strategy, a manufacturer can consider implementing single or multiple points of control for a specific CQA, depending on the risk associated with the CQA and the ability of individual controls to detect a potential problem. For example, with sterilised drug substances or biotechnological/biological products, there is an inherent limitation in the ability to detect low levels of bacterial or viral contamination in the drug substance. In these cases, end-product testing is considered to provide inadequate assurance of quality, so additional points of control (e.g., attribute and in-process controls) are incorporated into the control strategy.

The quality of each raw material used in the manufacturing process should be appropriate for its intended use. Raw materials used in operations near the end of the manufacturing process have a greater potential to introduce impurities into the drug substance than raw materials used upstream. Therefore, manufacturers should evaluate whether the quality of such materials should be more tightly controlled than similar materials used upstream.

6.2 Submission of Control Strategy Information

The information provided on the control strategy should include detailed descriptions of the individual elements of the control strategy plus, when appropriate, a summary of the overall drug substance control strategy. The summary of the overall control strategy can be presented in a tabular format as well as in a diagrammatic format, to aid visualisation and understanding (see Example 5 for example of a Control Strategy Summary in tabular form). Ideally, the summary should explain how the individual elements of the control strategy work together to assure drug substance quality.

ICH M4Q recommends that the individual elements of the control strategy reported in an application be provided in the appropriate sections of a submission, including:

- Description of Manufacturing Process and Process Controls (3.2.S.2.2);
- Control of Materials (3.2.S.2.3);
- Controls of Critical Steps and Intermediates (3.2.S.2.4);
- Container Closure System (3.2.S.6);
- Control of Drug Substance (3.2.S.4).

7 Process Validation/Evaluation

7.1 General Principles

Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a drug substance or intermediate meeting its predetermined specifications and quality attributes (ICH Q7). Process validation involves the collection and evaluation of data, from the process design stage throughout production, that establish scientific evidence that a process is capable of consistently delivering a quality drug substance.

The drug substance manufacturing process should be validated before commercial distribution of resulting drug product. For biotechnological processes, or for aseptic processing and sterilisation process steps for drug substances, the data provided in support of process validation is included as part of the marketing application (3.2.S.2.5). For non-sterile drug substance processes, results of process validation studies are not normally included in the dossier.

Generally, process validation includes the collection of data on an appropriate number of production batches (see ICH Q7, Section 12.5). The number of batches can depend on several factors including but not limited to: (1) the complexity of the process being validated; (2) the level of process variability; and (3) the amount of experimental data and/or process knowledge available on the specific process.

As an alternative to the traditional process validation, continuous process verification (ICH Q8) can be utilised in process validation protocols for the initial commercial production and for manufacturing process changes for the continual improvement throughout the remainder of the product lifecycle.

7.2 Principles Specific to Biotechnological/Biological Products

For biotechnological/biological products, the information provided in the dossier in support of process validation usually contains both commercial-scale process validation studies and small-scale studies. Process validation batches should be representative of the commercial process, taking into account the batch definition as detailed in the process description

The contribution of data from small-scale studies to the overall validation package will depend upon demonstration that the small-scale model is an appropriate representation of the proposed commercial scale. Data should be provided demonstrating that the model is scalable and representative of the proposed commercial process. Successful demonstration of the suitability of the small-scale model can enable manufacturers to propose process validation with reduced dependence on testing of commercial-scale batches. Data derived from commercial-scale batches should confirm results obtained from small scale studies used to generate data in support of process validation. Scientific grounds, or reference to guidelines which do not require or specifically exclude such studies, can be an appropriate justification to conduct certain studies only at small scale (e.g. viral removal).

Studies should be conducted to demonstrate the ability of the process to remove product-related impurities, process-related impurities (ICH Q6B) and potential contaminants (such as viruses in processes using material from human or animal origin, see ICH Q5A). Studies carried out to demonstrate the lifetime of chromatography columns can include experimental studies carried out in small-scale models but should be confirmed during commercial-scale production.

The limit of in vitro cell age for commercial production should be assessed. ICH documents Q5B and Q5D provide further guidance for relevant products.

When platform manufacturing experience is utilised, the suitability of the control strategy should be demonstrated and the drug substance manufacturing process should be appropriately validated at the time of marketing authorisation application. Full scale validation studies should include data derived from the final manufacturing process and site(s) used to produce the product to be commercialised.

8 Submission of Manufacturing Process Development and Related Information In Common Technical Documents (CTD) Format

The use of an enhanced approach to process development results in the generation of information for which a location in the CTD is not defined. Process development information should usually be submitted in Section 3.2.S.2.6 of the CTD. Other information resulting from development studies could be accommodated by the CTD format in a number of different ways and some specific suggestions are provided below. The applicant should clearly indicate where the different information is located. In addition to what is submitted in the application, certain aspects (e.g., lifecycle management, continual improvement) of this guideline are handled under the applicant's pharmaceutical quality system (see ICH Q10).

8.1 Quality Risk Management and Process Development

Quality risk management can be used at different stages during process development and manufacturing implementation. The assessments used to guide and justify development decisions (e.g., risk analyses and functional relationships linking material attributes and process parameters to drug substance CQAs) can be summarised in section 3.2.S.2.6.

8.2 Critical Quality Attributes (CQAs)

The CQAs of the drug substance should be listed, and the rationale for designating these properties or characteristics as CQAs should be provided in the manufacturing process development section of the application (3.2.S.2.6). However, detailed information about structural characterisation studies that supports the designation of these properties or characteristics as CQAs should be provided in the appropriate CTD format sections (e.g., 3.2.S.3.1, Elucidation of Structure and other Characteristics, 3.2.S.7 Stability). Some discussion of drug substance CQAs as they relate to drug product CQAs can be appropriate in the pharmaceutical development section of the application (3.2.P.2.1, Components of the Drug Product).

8.3 Design Space

As an element of the proposed manufacturing process, the design space(s) can be described in the section of the application that includes the description of the manufacturing process and process controls (3.2.S.2.2). If appropriate, additional information can be provided in the section of the application that addresses the controls of critical steps and intermediates (3.2.S.2.4). The manufacturing process development section of the application (3.2.S.2.6) is the appropriate place to summarise and describe process development studies that provide the basis for the design space(s). The relationship of the design space(s) to the overall control strategy can be discussed in the section of the application that includes the justification of the drug substance specification (3.2.S.4.5).

8.4 Control Strategy

The section of the application that includes the justification of the drug substance specification (3.2.S.4.5) is a good place to summarise the overall drug substance control strategy. However, detailed information about input material controls, process controls, and control of drug substance should still be provided in the appropriate CTD format sections (e.g., description of manufacturing process and process controls (3.2.S.2.2), control of materials (3.2.S.2.3), controls of critical steps and intermediates (3.2.S.2.4), drug substance specification (3.2.S.4.1)). The evolution of the control strategy should be described in the manufacturing process development section of the application (3.2.S.2.6).

9 Lifecycle Management

The quality system elements and management responsibilities described in ICH Q10 are intended to encourage the use of science-based and risk-based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle. Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation.

The development and improvement of a drug substance manufacturing process usually continues over its lifecycle. Manufacturing process performance, including the effectiveness of the control strategy and suitability of any design spaces, should be periodically evaluated. This can be done as part of the Product Quality Review described in ICH Q7 Section 2.5. Knowledge gained from this product quality review, as well as from the manufacturing of the drug substance for commercial supply, can be used to further improve process understanding and process performance and to adjust the control strategy to ensure drug substance quality. Knowledge gained from other products, or from new innovative technologies, can also contribute to these goals. Continual improvement and successful process validation, or continuous process verification, call for an appropriate and effective control strategy.

There should be a systematic approach to managing knowledge related to both drug substance and its manufacturing process throughout the lifecycle. This knowledge management should include but not be limited to process development activities, technology transfer activities to internal sites and contract manufacturers, process validation studies over the lifecycle of the drug substance, and change management activities. The knowledge and process understanding should be shared across all sites involved in manufacturing the drug substance (ICH Q10 1.6.1).

An applicant can include in the original submission a proposal for how specific future changes will be managed during the product lifecycle. For an example of how process parameters can be managed for a biotechnological product, see Example 2.

Any proposed change to the manufacturing process should be evaluated for the impact on the quality of drug substance and, when appropriate, drug product. This evaluation should be based on scientific understanding of the manufacturing process and should determine appropriate testing to analyse the impact of the proposed change. For chemical entities the appropriate testing to analyse the impact of the proposed change could, for example, be on an intermediate or drug substance. For process changes for biotechnological/biological products, see also ICH Q5E.

All changes should be subject to internal change management processes as part of the overall Quality System. This includes movements within the Design Space, which do not require approval by regional regulatory authorities.

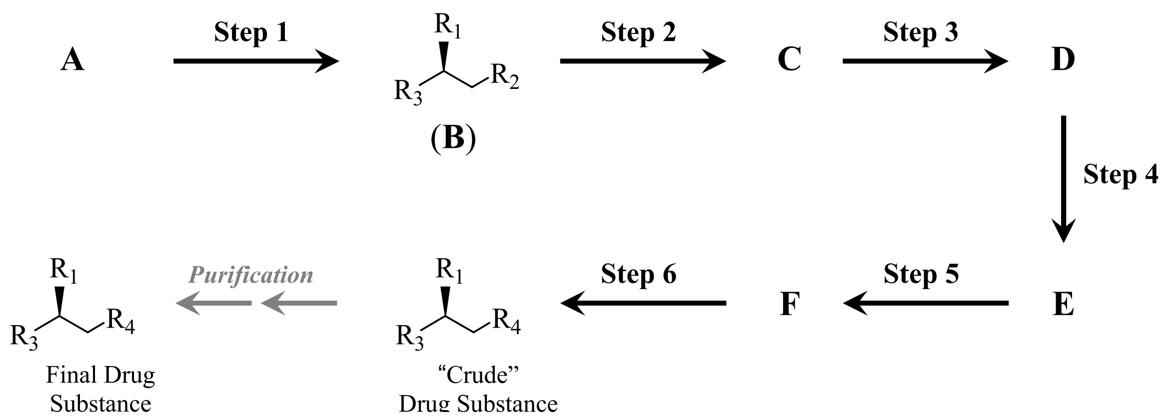
Changes to information filed and approved in a dossier should be reported to regulatory authorities in accordance with regional regulations and guidelines.

10 Illustrative Examples

These examples are provided for illustrative purposes and only suggest potential uses. This Appendix is not intended to create any new expectations beyond the current regulatory requirements.

10.1 Example 1: Linking Material Attributes and Process Parameters to Drug Substance CQAs - Chemical Entity

This example illustrates development of a design space using prior knowledge and chemistry first principles. It depicts both a traditional and enhanced approach to determination of the ranges for parameters controlling the formation of a hydrolysis impurity during Step 5 of the following reaction scheme (Also used in Example 4).



After the formation of intermediate **F** in Step 5, the mixture is heated to reflux. During reflux an impurity is formed through hydrolysis of intermediate **F**.

For the purpose of this simplified example, this is the only reaction of intermediate **F** that occurs during this reflux. The following assumptions where used in the design of the process:

- The concentration of intermediate **F** remains approximately constant.
- Temperature remains constant.
- The acceptance criterion for the hydrolysis impurity in Intermediate **F** is 0.30%. (This is based on the CQA in the drug substance and the demonstrated capacity of the subsequent steps to purge the impurity.)
- The initial amount of water in the reflux mixture depends on the amount of water in Intermediate **E**, which can be controlled by drying.

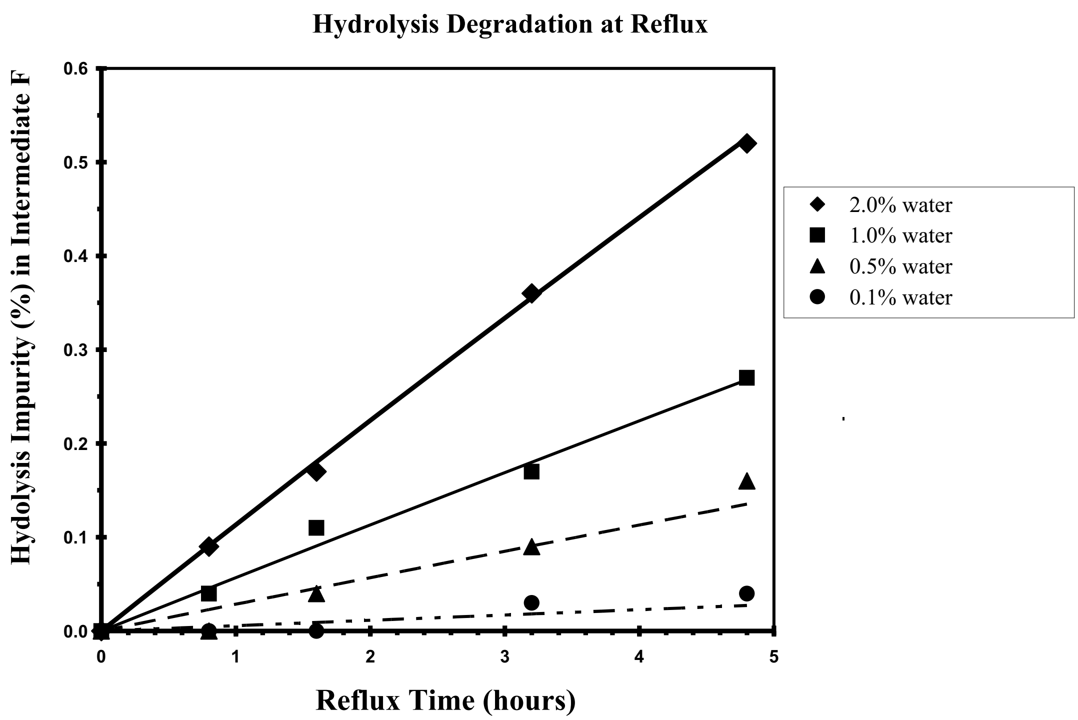
Time of reflux and water concentration were identified as the most important parameters affecting the hydrolysis of intermediate **F**. Other potential factors were determined to be insignificant based on prior knowledge and risk assessment.

The reaction was expected to follow second-order kinetics according to the equation below:

$$\frac{d[hydrolysis\_impurity]}{dt} = k[H_2O][F]$$

Where $[F]$ refers to the concentration of intermediate **F**.

Through simple experimentation the following graph linking the extent of hydrolysis to time and the water content of intermediate **E** can be generated:



<u>Traditional Approach:</u>

In a traditional approach this information would be used to set a proven acceptable range for % water and time that achieves the acceptance criteria for the hydrolysis impurity of 0.30% in intermediate F. This is typically done by setting a target value and maximum such as:

- Dry Intermediate E to a maximum water content of 1.0%
- Target reflux time of 1.5 hours and a maximum reflux time of 4 hours

<u>Enhanced Approach:</u>

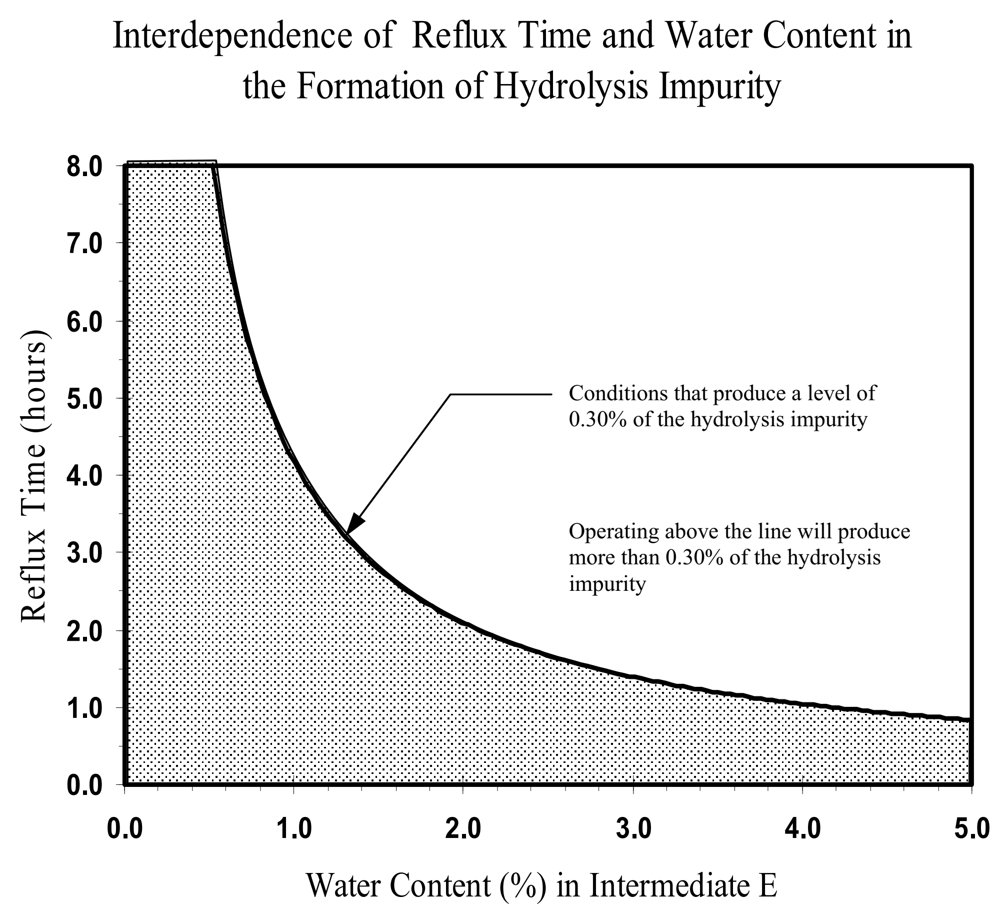
The 2nd order rate equation can be integrated and solved explicitly (Chemical Reaction Engineering, Levenspiel 2nd Edition, 1972).

$$\ln\left(\frac{M - X_F}{M(1 - X_F)}\right) = ([H_2O]_o - [F]_o)kt$$

Where:

$[F]_o$	refers to the initial concentration of intermediate **F**,
$[H_2O]_o$	refers to the initial concentration of water,
$M = [F]_o / [H_2O]_o$	refers to the ratio of the initial concentration of intermediate **F** to the initial concentration of water, and
X_F	refers to the time-dependent concentration of the hydrolysis degradant of intermediate **F**.

Solving this equation for time (t) permits the calculation of the maximum allowable reflux time for any combination of initial water content and target level for the hydrolysis impurity. (The initial concentration of intermediate **F** in the reflux mixture will essentially be constant from batch to batch.) The following graph shows the combination of conditions required to ensure that the hydrolysis impurity remains below 0.30% in intermediate **F**.



The area below the line in the plot above could be proposed as the design space.

Summary:

While both the traditional and enhanced approach provide ranges of water content and time to control the formation of the hydrolysis impurity, the enhanced approach allows more manufacturing flexibility.

10.2 Example 2: Use of Quality Risk Management to Support Lifecycle Management of Process Parameters

This example illustrates how results from an iterative quality risk assessment can be used to communicate the rationale for classification and proposed future management of changes to process parameters. Relevant parameters for establishment of a design space for a Q-anion exchange column are shown in this Risk Ranking Histogram. The histogram showing the ranking of parameters is intended for illustrative purposes only and is not all inclusive, nor is it meant to be applicable to all products that may use ion exchange chromatography.

Initial Filing

A quality risk assessment utilising prior knowledge and development studies can be used to rank process parameters based on their relative potential to have an effect on product quality if parameter ranges were changed. The histogram shows the potential impact to quality for future changes to parameter ranges based on the knowledge and understanding at the time of submission. Process development studies and interaction studies were conducted to establish design space boundaries for each of the higher risk parameters (parameters A-F) that impact CQAs. Parameters G, H and I were also challenged in the development studies and shown not to impact CQAs under the conditions studied. Changes to the ranges of these parameters could still carry residual risk (based on prior knowledge/uncertainties, including potential scale sensitivity). Parameters J-T were considered lower risk parameters based on documented prior knowledge, and therefore an impact on quality attributes is not anticipated. The ranking of parameters from the quality risk assessment can be used to communicate with regulators regarding a lifecycle management approach to assure continual improvement throughout the product lifecycle.

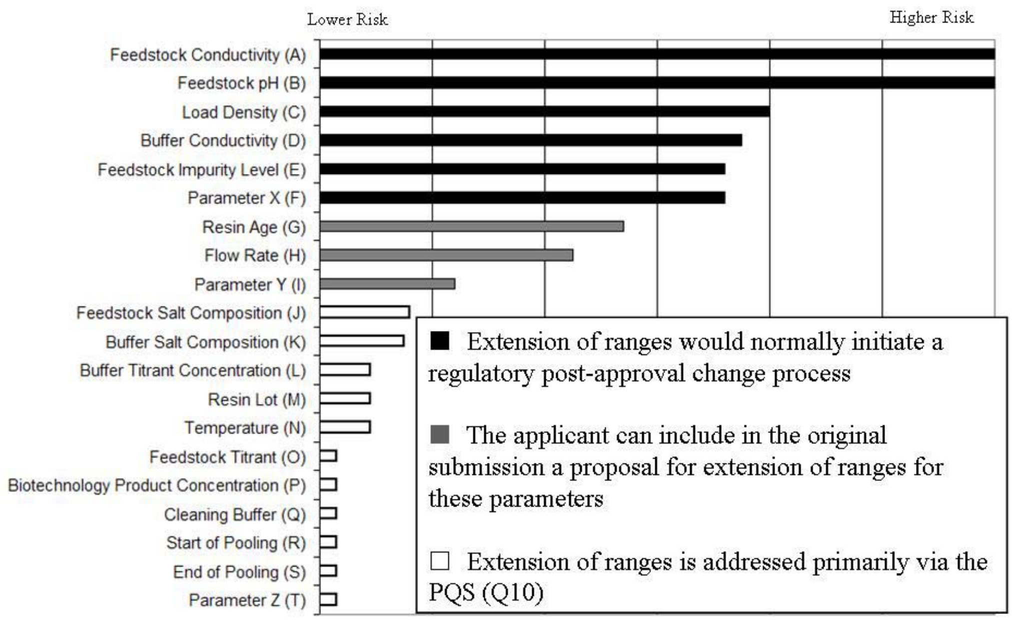
Lifecycle Management Options

Risk should be reassessed throughout the lifecycle as process understanding increases. Recommendations regarding lifecycle management changes can be found in the Pharmaceutical Quality System (PQS) as described in ICH Q10.

Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and consequently any extension of ranges for higher risk parameters (i.e. parameters A-F) would normally initiate a regulatory post approval change process.

An applicant can include in the original submission a proposal for how specific future changes to parameters G, H, and I will be managed during the product lifecycle. Extension of ranges for lower risk parameters (J-T) does not require prior regulatory approval, although notification may be called for depending on regional regulatory requirements and guidance. If it is determined subsequently to the filing that there is a change in the risk ranking, such that an extension of ranges for a parameter represents a higher risk, this change should be appropriately filed through the regional regulatory process.

Risk Ranking of Ion Chromatography Process Parameters



10.3 Example 3: Presentation of a Design Space for a Biotechnological Product Unit Operation

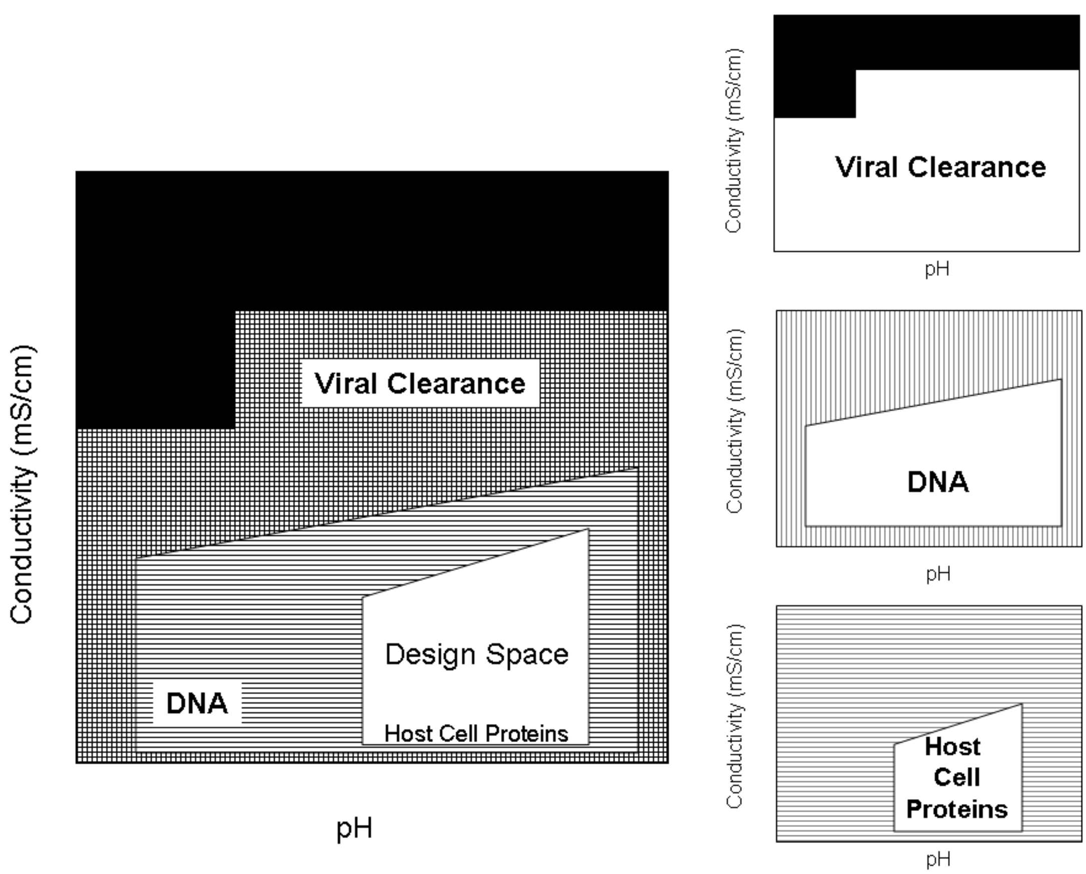
This example is based on a design space for a drug substance purification unit operation (Q-anion exchange column run for a monoclonal antibody in flow-through mode), determined from the common region of successful operating ranges for multiple CQAs. This figure illustrates a potential depiction of a design space based on successful operating ranges for three CQAs and the use of prior knowledge (platform manufacturing) in developing a design space. The ranges represented here indicate areas of successful operation and not edges of failure.

Viral clearance and host cell protein (HCP) ranges were derived from multivariate experimentation (see ICH Q8). The successful operating range for DNA was derived from prior knowledge (platform manufacturing) which in turn was derived from results of multivariate studies performed on related products. The successful operating range for HCP lies within the viral clearance and DNA successful operating ranges. In this example, the diagrams below show how HCP limits the unit operation design space compared to viral safety and DNA. Consideration of additional input variables, process parameters, or CQAs could limit design space further.

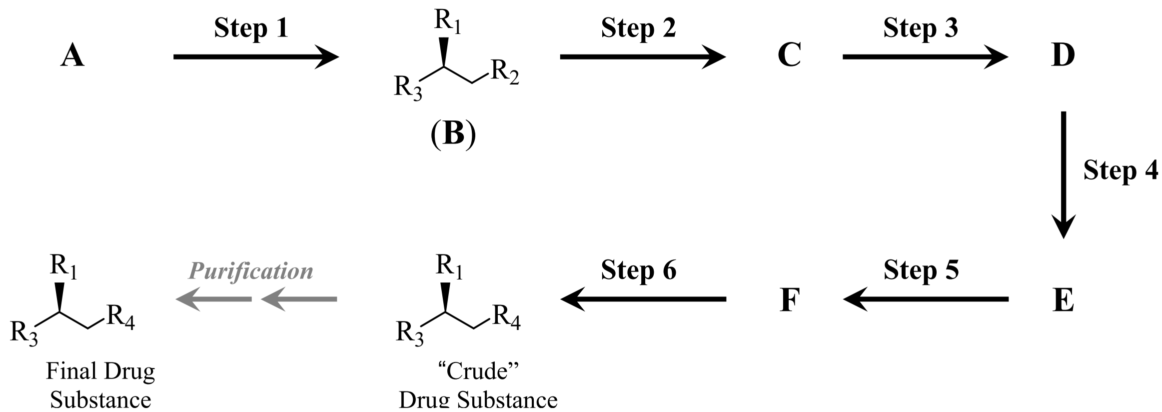
The design space is applicable only within specified conditions, including

1. Appropriately defined quality criteria for input materials;

2. Appropriately selected CQAs and process parameters.



10.4 Example 4: Selecting an Appropriate Starting Material



This example illustrates the importance of considering all general principles described in section 5.1.1 when selecting an appropriate starting material, rather than applying each general principle in isolation. The example is fictional, based on a linear synthesis for a relatively simple molecule, and is not intended to convey any particular meaning in relation to the number of steps.

The desired stereochemical configuration in the drug substance results from the synthesis of compound **B** in step 1 from a commercially available achiral precursor **A** and a stereo-selective reagent. A small amount of the opposite enantiomer of compound **B** is also formed in step 1. Once formed, both stereochemical configurations persist through the synthetic steps that follow, so the drug substance also contains a small amount of its undesired enantiomer as a specified impurity. In accordance with the principle that manufacturing steps that impact the drug substance impurity profile should normally be included in the manufacturing process described in section 3.2.S.2.2 of the application, it could be concluded that step 1 should be described in 3.2.S.2.2, and that **A** should be considered the starting material.

However, for this manufacturing process, it is also known that all of the significant impurities in the drug substance (other than opposite enantiomer) arise from steps 4, 5, and 6. Steps 2 and 3 have no impact on the drug substance impurity profile, and the only impact from step 1 is with regard to the enantiomeric impurity. Furthermore, it is also known that the stereocentre first formed in step 1 is stable to the manufacturing conditions in all of the steps that follow (i.e., no racemisation occurs or is ever likely to occur), and that a suitable analytical procedure exists for measuring the amount of the opposite enantiomer in compound **D**. Therefore, as compound **D** is in accordance with most of the other general principles described in section 5.1.1, it would be reasonable to propose **D** as the starting material instead of **A** in accordance with the principle that early steps in the manufacturing process tend to have a lower potential to impact drug substance quality than later steps. In this example, the only impact of step 1 is on the amount of the enantiomeric impurity in the drug substance, and this could alternatively be controlled through an appropriate limit on the amount of the opposite enantiomer in compound **D**. Information on steps 1-3 would be made available to regulatory authorities in order to justify such a proposal as per regional expectations.

A similar argument could be made if the stereocentre in the drug substance originated in the commercially available precursor **A** instead of being created in step 1.

10.5 Example 5: Summary of Control Elements for select CQAs

This example illustrates how part of a drug substance control strategy might be summarised in tabular form. The tables show how an applicant can communicate information on multiple elements of a drug substance control strategy and guide the reviewer to sections of the CTD where detailed elements of the control strategy are described or justified. Such control strategy summary tables should not contain the rationale or justification for the controls but should simply indicate where the information can be found in the application for marketing authorisation.

There are multiple ways of presenting this information, and two are shown below. One table shows more detail than the other to illustrate that there is a range of possibilities for presenting this information. The amount of detail included in a control strategy summary table is up to the applicant and is not related to the type of drug substance. CQAs and control elements shown in the tables below are only examples and are not intended to be a comprehensive representation of all elements of a drug substance control strategy. The tables should not be considered templates. The section of the application that includes the justification of the drug substance specification (3.2.S.4.5) is a good place to summarise the overall drug substance control strategy.

5a. Example of a Possible Control Strategy Summary – Biotechnological Products

Drug Substance CQA	**Control Strategy for drug substance CQA**	**Section(s) in CTD where detailed information is located**
Contaminants in biologically sourced materials (Viral Safety)	Summaries of viral safety information for biologically-sourced materials	3.2.S.2.3
	Detailed information including for materials of biological origin, testing at appropriate stages of production and viral clearance studies	3.2.A.2
Residual Host Cell Proteins	Design Space for an individual unit operation (e.g. see Example 3)	3.2.S.2.2
	Target range for consistent removal assured by validation	3.2.S.2.5
	Analytical procedures and their validation	3.2.S.4.2 and 3.2.S.4.3
Specific Glycoforms	Controls implicit in the design of the manufacturing process including a summary of process control steps (e.g. cell culture conditions, downstream purification, holding conditions etc.)	3.2.S.2.2
	Characterisation to justify classification as CQA (cross reference to non-clinical/clinical sections if relevant)	3.2.S.3.1
	Control of Critical Steps, Testing program and specifications	3.2.S.2.4 and/or 3.2.S.4.1
	Justification of specification	3.2.S.4.5
	Stability	3.2.S.7

5b. Example of a Possible Control Strategy Summary – Chemical Entity.

Type of Control → / Drug Substance CQA (3.2.S.2.6) / Limit in Drug Substance↓	In process Controls (including In-process testing and process parameters)	Controls on material attributes (raw materials/starting materials /intermediates)	Impact of Manufacturing Process Design	Is CQA tested on drug substance/ included in Drug Substance specification (3.2.S.4.1)
Organic Purity				
- Impurity X NMT 0.15%	Design space of the reflux unit operation composed of a combination of %water in Intermediate E and the reflux time in step 5 that delivers Intermediate F with Hydrolysis Impurity ≤0.30% (3.2.S.2.2)			Yes/Yes
- Impurity Y NMT 0.20%	Process parameters step 4 (3.2.S.2.2) $p(H_2) \geq 2$ barg T <50°C In-process test step 4 (3.2.S.2.4) Impurity Y ≤0.50%			Yes/Yes
- Any individual unspecified impurity NMT 0.10%		Specs for starting material D (3.2.S.2.3)		Yes/Yes
- Total impurities NMT 0.50%				Yes/Yes
Enantiomeric purity - S-enantiomer NMT 0.50%		Spec for starting material D (3.2.S.2.3) - S-enantiomer ≤0.50%	Stereocentre is shown not to racemize; (3.2.S.2.6)	No/No
Residual Solvent				
- Ethanol NMT 5000 ppm	In-process test during drying after final purification step (3.2.S.2.4) LOD ≤0.40 %		In-process results correlated to test results on drug substance. (3.2.S.2.6)	No/Yes
- Toluene NMT 890 ppm	In-process test step 4 (3.2.S.2.4) ≤2000 ppm by G.C		Process steps after step 4 are shown to purge toluene to levels significantly below (less than 10%) that indicated in ICH Q3C (3.2.S.2.6).	No/No[1]

[1]This approach could be acceptable as part of a control strategy when justified by submission of relevant process data that confirms the adequacy of the process design and control. The manufacturing process should be periodically evaluated under the firm's quality system to verify removal of the solvent.

Notes concerning Table 5b

The above table is based on the route of synthesis presented in Example 1. The Control for enantiomeric impurity is based on Decision Tree 5 from ICH guideline Q6A, which allows for control of chiral quality to be established by applying limits to appropriate starting materials or intermediates when justified from development studies. In order for this approach to be acceptable data would need to be provided in 3.2.S.2.6 to demonstrate the stability of the stereocentre under the proposed manufacturing conditions.

The table summarises only a portion of the control strategy that would be presented at the time of initial submission and does not include all CQAs of the drug substance. The example control strategy provides for control of some CQAs at stages in the process prior to the drug substance. The elements of the proposed control strategy described in the application would be justified by the applicant in 3.2.S.4.5 and subject to regulatory assessment and approval.

11 Glossary

Chemical Transformation Step

For Chemical Entities, a step involved in the synthesis of the chemical structure of the drug substance from precursor molecular fragments. Typically it involves C-X or C-C bond formation or breaking.

Continuous Process Verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)

Control Strategy: A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Critical Quality Attribute (CQA): A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8)

Design Space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8)

Intermediate: See ICH Q7, ICH Q3a, and ICH Q5c

Impurity: See ICH Q6A and ICH Q6B

Lifecycle: All phases in the life of a product from the initial development through marketing until the product's discontinuation (ICH Q8).

Platform Manufacturing: The approach of developing a production strategy for a new drug starting from manufacturing processes similar to those used by the same applicant to manufacture other drugs of the same type (e.g., as in the production of monoclonal antibodies using predefined host cell, cell culture, and purification processes, for which there already exists considerable experience)

Process Robustness: Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality. (ICH Q8)

Quality Risk Management (QRM) : A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9)

Quality Target Product Profile (QTPP): A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (ICH Q8)

Real Time Release Testing: The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls. (ICH Q8)